DCoE TBI Monthly Webinar
State of the Science: Clinical, Metabolic and Pathologic Effects of Multiple Concussions
Jan. 16, 2014 – 1-2:30 p.m. EST

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Thank you, Tammy. Good afternoon, everyone, and thank you for joining us today for the (inaudible) Traumatic Brain Injury January webinar. My name is Dr. Donald Marion. I am Clinical Affairs Senior Consultant for the Defense and Veterans Brain Injury Center and the Henry Jackson Foundation. I will be your moderator for today's webinar.

Before we begin, let's review some webinar details. Live closed captioning is available through Federal Relay Conference Captioning. Please see the pod beneath the presentation slides. Today's webinar is hosted using the Defense Connect Online or DCO platform. Should you experience technical difficulties, please visit dcoe.mil\webinars to access troubleshooting tips. If you cannot connect to DCO, please continue to listen via the phone, and go to DVBIC.dcoe.mil\online-education to download the slides. There may be an audio delay as we advance the slides in this presentation. Please be patient as the connection catches up with the presenter's comments.

During the webinar, you are welcome to submit technical or content-related questions via the Question box. We actually encourage that. The Question box is monitored and questions are forwarded to the moderator, which is me, for response during the question and answer session during the last half of the webinar. Our presenters will field as many questions as time permits.

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I will now move on to today's webinar topic, State of the Science Clinical, Metabolic and Pathologic Effects of Multiple Concussions. During the past few years, professional athletes and their families have become increasingly concerned about the long-term neurologic effects of repeat concussions. The premature deaths of several professional football players have drawn attention to the relationship of multiple concussions with neuro cognitive disorders that occur decades after these injuries. Although similar changes in the brain were associated with boxing and actually first described by Markland (sp) in the 1920s as punch drunk syndrome.

This webinar will examine the findings of laboratory and clinical studies on the mechanisms responsible for brain injury following one or multiple concussions. The presentation will address a particular focus on a class of proteins called HAL protein and the association of some of the histologic features of multiple concussions with those of Alzheimer's disease. At the conclusion of this webinar, participants will be able to describe the pathophysiology of concussions, summarize metabolic abnormalities caused by concussions and the window of vulnerability of the brain to a second concussion, identify the long-term changes in patterns of protein deposition possibly associated with multiple concussions, and articulate the possible association of multiple concussions with long-term cognitive deficits.

So, we are very pleased to have three distinguished presenters for today's webinar. Individuals I've known for quite some time and people that are, I think, perfect for their individual presentations in weaving a story for us today. And they are Dr. David Hovda, Dr. Clay Goodman, and Dr. Stephen Zukowski.

So, I would now like to introduce our first presenter, Dr. David A. Hovda. Dr. Hovda is Director of the UCLA Brain Injury Research Center and Professor of Neurosurgery and Molecular and Medical

Pharmacology at the David Geffen School of Medicine at UCLA in Los Angeles, California. Dr. Hovda is former President of the National Neurotrauma Society and Study Section Committee Chair for the National Institutes of Neurological Disease and Stroke. Dr. Hovda is well known for his translational work on the pathobiology of TBI, was the principal scientific consultant for the NICOE, and has done extensive work in multiple concussions, particularly in the boxing arena in California, so with that, I will turn it over to Dave.

Thank you, Dr. Marion. I want to commend the Defense and Veterans Brain Injury Research Center for helping us with this webinar presentation. My job today is to try to give you a very brief overview of the neurobiology of concussion and the consequences of repeat mild traumatic brain injury in the human brain. I will use examples from animal studies and also transfer over to human studies to give you a feeling for the translational work that is associated with this particular type of effort.

I have no comments or any problems with disclaimers.

So what is a concussion? It really is an injury to the brain that is caused by biomechanical forces. It's not a stroke. These forces can be direct or indirect, so you don't need a specific blow to the head. It actually can be thought of as a general brain movement injury. It results in regional and temporal cellular alterations and may produce cell death. It produces a state of energy crises and subsequent metabolic dioskesis (sp). The term dioskesis is used by many neurologists, and it simply means that areas of the brain that are disrupted or dysfunctional that won't go on to die but that are responsible for deficits that slowly begin to recover over time.

Fundamentally, after mild traumatic brain injury, or any severe traumatic brain injury, it changes the priority for fuel, and as outlined by Dr. Marion and will be addressed by other speakers, it may contribute to chronic neurological degeneration related to disease.

The human body, and the human brain, run on energy. The human brain only has about two percent of the mass of the human body but it takes up 20% of its energy. It runs on several types of fuels that generate energy through adenosine triphosphate. And you can think of this as a very high energy demanding organ.

There are some fun facts about adenosine triphosphate in terms of the cost of living. So you run on about 522 amps per second. You make about 65 kilograms of ATP per day. The human being consumes about 380 liters of oxygen per day. And your human brain works on about 116 watts of power. That's kind of light a dim light bulb.

If we take the human brain and we placed it within the skull, which is our natural born helmet, and we look at it from the standpoint of consistency, there are many, many studies that have been done over the years that relate to the biomechanics and engineering with regard to traumatic brain injury. So the human brain actually has the consistency of undone Jell-O. It is encased within a leather sac called the dura matter. And you can think of it as floating to some degree within the human skull.

This particular illustration, if we exposed this human brain to an injury, that being a blast, what would happen is that the happen, or the head, is actually moved violently forward and the brain is moved violently back. This causes an injury from the impact from the brain slamming against the inside of the skull and causes a vacuum or a contrecoup injury in the front part of the skull. As this process continues over time, this slamming of the brain back and forth within the skull can create problems and distortions which are resulting in dysfunction of the human brain.

A lot of times people talk about the injury being the fact that the brain actually collides within the skull, but what's more important for our topic today is that different parts of the brain have different consistency, and consequently when the brain is moved violently, different parts of the brain are moved at different rates.

So as the brain moves back and forth, you can see as the different parts of the brain will rotate and causes sheer stress zones in different parts, which can result in a dysfunction or disconnection, or even cell death.

So this example of the blast in front shows now how the brain can be moved back and forth, and the blue arrow within the skull can show how different parts of the brain can be moved, and you can see in this particular cartoon how the neck is actually manipulated back and forth.

So what one needs to understand is that the human brain has two hemispheres. It's connected by a connection called the corpus callosum. It has grey matter and white matter. And that these two parts of the brain or different parts of the brain have different consistencies. And these consistencies turn and rotate at different rates.

So it's really a brain movement injury. The brain is violently moved and stretched within the skull. And that's the most important thing to remember when we're talking about a concussion.

If we were to take a cartoon of a neuron, and this cartoon is called a neurometabolic cascade and potassium and glutamate flux, and we actually hit the neuron with a hammer, or in this case a concussion, what happens is that all the neurons in the central nervous system fire, they discharge. It's like having a mini seizure. Of all the neuro transmitters that are released, one in particular, glutamate, is an excitatory amino acid that binds onto a receptor called the NMDA receptor. And this NMDA receptor causes a release of potassium outside the cells. When potassium is released outside the cells, the central nervous system shuts down. This is because it causes a depolarization of the central nervous system. And cells within the brain work on electricity. What this results is that Mother Nature has a very good way of taking care of this, and she does this by activating pumps which drive the potassium back in. This pump is called the sodium potassium pump, and it is driven by ATP, and is primarily supported by glucose. So there's a very high energy demand at the moment of concussion, and that this creates the first part of what is called an energy crises.

Now along with potassium coming in, calcium comes rushing into the cell. And calcium can be very damaging to the cell. It can actually cause cell death and protease activation. But Mother Nature has a way of dealing with this as well. What it does is it has the intracellular calcium buffered by the mitochondria. Well the problem is is the mitochondria is the part of the machinery of the cell that makes the energy. So you have a high need for energy but you can't make it because your energy factory is actually being kind of clogged up by calcium.

Now if we look at the connections from different parts of the brain, which are caused the axons, this calcium actually produces neuro inflammation, axonal swelling, and can cause impaired axonal transport, and actually myelin damage.

So you have a really high need for energy, you can't make the energy, and the connections that are involved in between different parts of the brain are compromised, and therefore the human brain has a difficult time working. This probably is one of the reasons why you have some of the disconnections that you see or that result in symptoms after a concussion, all that from amnesia to unconsciousness to (inaudible) to lethargy and all the other disturbances that would commonly refer to as the post-concussive syndrome.

If we look at this in animals, so this is an animal, a rat, which is cut from the top down, and the black area points to an area of the brain. And this particular image is an image called the 2-deoxyglucose autoradiographic image, which looks at the acute (inaudible) or use of glucose, so red is higher than green or blue. And the arrow points to where the concussion occurs, and you can see that there is a big red area around the cerebral cortex. If we follow this over time, in the single animal over time, and we look at time in terms of hours, at the bottom, to days, and on the Y axis we look at the amount of glucose metabolism, we can see that at the moment of concussion there's this high energy burn. And then the brain gets exhausted and it goes into a state of metabolic depression, and this depression can last for about ten days.

It's very important to understand that these two periods, this hyper burning or hyperglycolosis, and this metabolic depression, or metabolic dioskesis, really is not injury severity dependent. This occurs in mild, moderate or severe injuries in animals, but it appears to be the length of time that you stay in these states that's related.

If you combine all the different parts of all the different neurochemistry and all the different metabolism and all the typical imaging studies that have been done experimentally throughout the world, and you look at this from the standpoint of the different cascades following a single mild traumatic brain injury, what you end up seeing is a figure like this which is after time in minutes to hours to days, there are different things that are changed in terms of increases or decreases compared to control in different parts of the brain. Consequently, symptom natology (sp) after traumatic brain injury, or after mild traumatic brain injury, can change. You may not show the symptoms immediately. You may have to wait for a period of time before you actually see them because of this ongoing cascade.

Please remember that this cascade is not only temporally involved, as it's depicted here, but it's also regional, just as I depicted in the cartoons before. So it could be different in the frontal lobes, or the temporal lobes, or the cerebellum, or in the deep structures of the brain.

Now here's a fascinating study. If you looked at this from the start of – this is another animal study. If you look at the top, or the control, if you just emulate the cortex of any organism, in this case it's a rat, and you look at the left side you see an increase in glucose metabolism, and on the right image you see an increase in blood flow. This is coupling. So whenever the human brain, or whenever the brain needs metabolism to support itself due to activity, it increases its glucose metabolism. And in order to deliver that fuel, it increases its blood flow.

So now let's look under the white line and look at six hours post and three days post following concussion. We can again stimulate the brain, but now if you look on the right side, there's no increase in cerebral blood flow. So there's an enormous energy demand for the brain, but I can't get the energy because the mitochondria is clogged up with calcium, and now I'm having a hard time getting the fuel to the brain because the blood flow is not increased appropriately and we've lost coupling.

What happens if we have a second concussion during the time when this brain is depressed? Well, when this happens, if you look at this particular figure where we look at the first blue line, this is the first single insult in a very young animal which has a very mild traumatic brain injury. If we give it a second concussion while it's depressed after day one, now you see this red line which lasts for a much, much longer period of time. If we wait for this cascade to abate over the course of days and then provide, say, a third concussion, this third concussion now looks more like the first concussion. So there's this window of time after injury which appears to be different whether you're young or old, or whether you're a female or a male. And given the time I can't go into details on why that's the case, but that is truly the case.

So with the rodent, single concussion causes temporary changes in brain chemistry and cerebral metabolism, temporary deficits in memory and learning. It enhances the vulnerability to post traumatic stress and to Parkinson's disease.

In repeat concussions in the rodent model, you can have increased axonal injury, you can have memory deficits that last longer, and the interval between injuries is critically important in whether the metabolic markers are cumulative. In addition, an interesting finding is pituitary functions and corresponding hormonal deficits occur with these repeat concussions.

If we go to the next slide, we look at individuals, these are human beings now, who we've actually studied them using positron emission tomography. And now if you look at the bottom scale, you look at days to months, and this is severe head injury. But if you look at this, you can see an increase in burning on the first left-hand image for the patch. The very top is the nose, the back. The bottom is the back of the head. And you can see it's bright red where it burns a lot. And then the brain goes into a state of metabolic depression or dioskesis and slowly recovers over time, just like in the animals.

And just like in the animal studies, if we look at the relationship between the increase in glucose metabolism in the top frames with the animals, you can see an increase in glucose metabolism but no increase in cerebral blood flow, so the areas are uncoupled. In human traumatic brain injury, we have the same effect, that we have an increase in metabolic demand but we have no increase in stream of blood flow, so it's uncoupled.

But what about concussion? On the right-hand side you see a normal UCLA undergrad student, with the top of the scan being the nose and the back being the back of the head, and you see a normal distribution of glucose metabolism. I was called by the physician for the football team who said, We have a concussion patient, would you like to image him. And I said, Of course, and so I went over and I walked this patient back to the hospital, and we kept him overnight. And we scanned this individual, who is a middle linebacker, who had no loss of consciousness, knew exactly where he was, could tell me his classes, and who was president of the United States and what he wanted to do. He just didn't want this information to go out to the Combine because he wanted to be an NFL player.

That same day I happened to have a severe head injured patient, and we scanned those two patients side by side, and how you see that, in fact, the concussion patient looks identical to the severe injured patient in terms of the depression longer term after the injury. Just like the animals. So just like the animals, it's not the severity of the injury that causes the brain to go into this metabolic and neuro chemical cascade, it's the length of time that they stay in these different events that causes the problem.

This has been replicated by many people, both in Pittsburgh and at Cambridge, but also in Italy, where Vagnosi (sp) and his colleagues looked at patients that were athletes that just had a single concussion. And here what we took about repetitive injury and return to normal activity slide, these are individuals who are athletes who had had a concussion, and these investigators were looking at magnetic resonance imaging using a way of looking at spectroscopy. Spectroscopy is just a way of looking at the imaging the neuro chemistry within different regions of the brain.

So if we look at the left part of this particular slide, you can see these black bars. And the first black bar that you see on the left is a control individual. The second black bar is at three days, and then 15 days, and 30 days. So this is after a concussion, these individual athletes, who some of them played European football, some of them played rugby. They had a single concussion. What happens is that this black bar goes down. And this black bar represents a ratio between any (inaudible) creatinine, which is a way of marking the (inaudible) marker for the viability of the cells, particularly it involves the mitochondria.

All these players were asked not to return to play. But just as is usually the case with all athletes, and with many military personnel, is that they go against the recommendation. They say, I'm fine, I want to go back into play. A few of them did, and in the right-hand panel you begin to see these individuals that had received a second concussion before they had recovered from the first concussion. Now these black bars are down out to 45 days. So the same principle holds, both for animals and for humans, with regards to repeat concussions.

So in closing, what is the cerebral concussion? Well, first of all it is caused by biomechanical forces. It is not cerebral ischemia or stroke. These are much different entities. And it's very dangerous to try to apply what we've learned of stroke or ischemia directly to traumatic brain injury. There certainly is overlap, and we can certainly complement those findings, but traumatic brain injury has its unique path of physiology and its neurobiology. It results in a regional and temporal cellular dysfunction including cell death. In areas that survive, it produces a state of energy crises and a subsequent metabolic dioskesis. Surviving brain cells alter their use of fuels. I didn't get a chance to go into this in great detail, but, in fact, glucose may not be the primary fuel for individuals after concussion. So instead of giving somebody a, say, a chocolate bar after a concussion to recover, we may want to give them something else because the brain is using that fuel for things other than the pumping mechanism that we want it to use for.

Surviving brain cells (inaudible) fuels and can exhibit long-term dysfunction. And it has been written and discussed by many individuals, the University of Texas at Galveston and also Houston, that traumatic brain injury needs to be now thought of as a disease, not necessarily an event that you recover from.

So with that I thank you very much, and I'll turn it back to the moderator. Thank you, Dr. Marion.

Dave, thank you. And just for everyone on the line, that was huge. And what you've done, David, is really laid the metabolic and physiologic underpinning for the acute effects of concussion, especially this whole notion that blood flow is insufficient to meet the metabolic needs of the brain, but also very clearly and nicely shown us why a second concussion before a full recovery from the first is so bad. And so I hope the providers out there for our service members are listening carefully to this and pay attention to that because that's the rationale for the 50 meter rule and for keeping your guys out once they've had a concussion for at least 24 hours. So very much appreciate it, Dave.

So that's kind of what's going on in the first few hours and days after the injury, but there are some insidious processes that also are happening, and I'm very proud to introduce our second presenter, Dr. Clay Goodman, who is Professor and Associate Dean of Pathology and Immunology and Neurology Departments at Baylor College of Medicine in Houston, Texas. Dr. Goodman trained at Baylor and National Naval Medical Center in Bethesda where he did his residencies, (inaudible) both in neurology and neuropathology, and his areas of interest are cellular and molecular basis for neural injury and recovery of TBI.

He was asked to, I believe, co-Chair a special NIH committee or workshop on chronic traumatic encephalopathy in December or November of 2012. And I went to that workshop and I was really impressed by his talk and his understanding of TAL protein, which is sort of, we think, the underpinning of chronic traumatic encephalopathy and the prolonged effects of multiple brain injuries, so I thought it was most appropriate that Dr. Goodman present next. So with that, Clay, I'll turn it over to you.

Okay. Thank you, Dr. Marion. Yes, we're going to focus in this segment on TAL, which is a protein common to several neurodegenerative diseases as well as chronic traumatic encephalopathy.

I have no financial disclosures or conflict of interest.

So first let's consider the protein tau. It is an abundant, intracellular microtubule-associated protein. So it's associated with the situs skeleton of the neuron. And it participates in microtubule assembly, stabilization and spacing. The tau molecule carboxy end binds the microtubule and the amino terminal portion of the molecule sticks out from the microtubule and assists in spacing the microtubules appropriately.

There are several isoforms of tau that occur due to differential splicing and that are under different developmental control.

Now one might think that tau is an extraordinarily important protein, and it is, but if you knock it out in mice, they're, frankly, asymptomatic, so other proteins can do this function.

The problem with tau is, and several of the other pathogenic proteins we may touch on, is that if it becomes hyperphosphorylated, that diminishes its interaction with microtubules.

Tau, when hyperphosphorylated, has less interaction with microtubules and a greater probability of interacting with itself. So the tau may aggregate within the cytoplasm of the neuron, or the cytoplasm of astrocytes, to give neurofibrillary tangles. And, as I mentioned, hyperphosphorylation leads to a decline in interaction with the microtubules. Filamentous aggregates form within the cytoplasm. And, in addition, if the tau misfolds, that may also facilitate hyperphosphorylation by exposing amino acid residues that are prone to phosphorylation.

Now one of the recent, quite fascinating, observations is that misfolded tau may interact with normal tau to template, or in a prion-like manner, cause the native TAL to mis-fold. So this is very reminiscent of what's going on in the prion diseases, like Creutzfeldt disease and mad cow disease in which a misfolded protein is basically subverting and transforming a normal protein into the abnormal isoform.

As a corollary of this templating is also the spread of neurofibrillary tangles. And as Dr. Zukowski will describe in the Alzheimer disease segment, in Alzheimer's disease there is a very stereotyped spread of neurofibrillary tangles in the brain. In CTE we don't see that, but we do see spread, and we have to address how that could happen.

Now we see tau forming neurofibrillary tangles in several neurodegenerative disorders called the tauopothies. And what I like to call the pure tauopothies are those in which tau is really the dominant protein. And these include the classical disease Pick's Disease, which is now known more broadly as frontal temporal lobe (inaudible) degeneration. There are some less common diseases like progressive super nuclear palsy and corticobasal degeneration. And quite importantly for us today, is that tau appears to be the major protein player in chronic traumatic encephalopathy.

Now we will be speaking later about the relationship of CTE to Alzheimer's disease, and Alzheimer's disease can be thought of as a mixed proteinopathy in which beta amyloid is a major player predominantly in the extra-cellular space and tau is the major player in the intracellular space.

And this leads us to the concept of fibrillogenesis, which is that an abnormal protein is produced by some mechanism, and that as it accumulates, it aggregates into fibrils and ultimately filaments and inclusions that can actually be seen initially by electron microscopy and then later by light microscopy as the burden of abnormal protein increases. And that this accumulation of misfolded protein may contribute to cellular dysfunction and cellular death.

Now in the normal cell, protein misfolding actually happens quite frequently. During protein synthesis, you know, we normally think of protein synthesis as being relentlessly efficient like a Mercedes-Benz automotive factory, but in fact anywhere from 30 to 40% of proteins misfold. And they have several potential fates. One is to undergo autophagy and lysozomes, so they are simply degraded and the amino acids are reused. There's also an apparatus in the cell called the proteozyme which will accumulate abnormally folded proteins which have been marked by a variety of marker proteins like Ubiquitin. And the proteozyme will attempt to refold the protein or give the protein an opportunity to fold to the native state. And if it fails to do that, then the protein will be degraded.

The most pathogenic potential fate of misfolded proteins is to aggregate or polemarize, to form fibrils which accumulate and ultimately form an intracellular inclusion. It's thought that the fibrils, which are long, pointy, sharp collections of protein, contribute to the cellular injury.

Now I would like to pause at this moment and point out that autophagy and proteozymal processing are heavily energy-dependent processes, so protracted metabolic bioenergetic compromise, such as Dave described, could contribute to accumulation of misfolded protein.

Now the misfolded protein can occur randomly, by chance. So as we see in the first side of the slide a little red dot with a kind of a Pacman appearance, this is a misfolded protein of TAL, or some of the other misfolded proteins. The others in green are the normal form. And under normal circumstances that misfolded protein would be degraded by autophagy or proteozymal degradation.

However, if there is a failure to degrade, such as might occur in energy failure or in some families there's a genetic propensity for these proteins to misfold, then you have potential for accumulating the misfolded protein. And if sufficient amounts of the misfolded protein accumulate, that protein can begin to interact with the normal ISO form of the protein to transform it in a prion-like fashion, through templating, to create more of the abnormal protein. So a self-replicating cycle is now initiated. And these abnormal proteins are hyperphosphorylated, tend to aggregate, and, hence, you get misfolded protein aggregates leading to neurofibrillary tangles.

These can be seen by electron microscopy as elongate fibrils accumulating within the neuron. These fibrils may accumulate to ultimately form a structure called a neurofibrillary tangle, which occupies the cytoplasm of the neuron, seen on this side of the slide by H and E, and then on this side in a silver stain. Nowadays we can use immunohistochemistry to detect this. But you can see it basically fills the space of the cytoplasm and interferes with cellular function and ultimately leads to cellular death.

Now we also indicated that neurofibrillary tangles spread. Pathogenic tau can convert native tau to pathogenic tau through templating. And then it appears that there is neuron-to-neuron dissemination, particularly in Alzheimer's disease where there is this stereotyped dissemination of neurofibrillary tangles. We don't know exactly how this dissemination occurs. Some believe it may be trans-synaptic so some of the pathogenic protein is released when neurotransmitters are released. We also know that going on all the time is release of microvesicles, also known as exozomes, which allow little particles of cytoplasmic constituents to bleb off the neurons and float into the extracellular space and merge with another cell. A great deal of attention is being paid to exozomes now.

A corollary of this is that any process that increases exozome release of pathogenic tau could facilitate the spread of the pathogenic tau isoforms.

So what does all of this have to do with traumatic brain injury? Well we know, as Dr. Hovda described, axonal injury occurs during the biomechanical deformation of the brain during blast and sporting injuries. From the work of John Pavlishock looking at the ultra structure of diffuse axonal injury, there is microtubule spacing collapse. Basically the tau is dislodged from the microtubules and the situs skeleton collapses leading to release of free tau which has fewer constraints against misfolding. And once it starts to misfold, it may become hyperphosphorylated, which decreases the chances of reattachment to the microtubules and increases the probability of aggregation and templating.

Also it's been demonstrated that when axonal injury occurs, there is increased neuronal blebbing and exosome release so there is potential for release of this abnormal ISO form. And clinical studies have demonstrated increased levels of serum and CSF tau in boxers. We see increased CSF TAL in severe traumatic brain injury, and also increased extracellular tau has been demonstrated in TBI by microdialysis. So there is a potential mechanism for dissemination of the pathogenic isoform.

And we know that diffuse axonal injury is a process, not an event. The axon is injured, and then there is accumulation of axoplasm, and ultimately there may be separation of the ends of the axon with release of TAL and amyloid into the extracellular space. And here we see in a blast injury patient neuronal axonal retraction balls, and at these sites we expect there would be release of pathogenic ISO forms.

So traumatic brain injury appears likely to shift the probability that TAL will misfold, template, aggregate, and spread. And the possible clinical correlations of this is chronic traumatic encephalopathy. This was mentioned earlier this was clinically described as punch drunk syndrome in the 1920s. In the 1970s, neurofibrillary tangles were recognized as being the pathological hallmark of punch drunk syndrome, or known more elegantly is dementia pugilistica. And then in the 2000s, chronic traumatic encephalopathy. And it does appear the CTE has a unique distribution of tau neurofibrillary tangles.

The clinical features of chronic traumatic encephalopathy include cognitive decline, decline in memory, decline in the executive function with explosivity and impulsivity. There is motor decline, often with extrapyramidal or Parkinson-like features. And neuropsychiatric findings of affective changes including depression, anxiety, and as I mentioned earlier, the personality changes of explosivity.

What is seen pathologically are hyperphosphorylated tau inclusions, which, rather than being in the distribution seen in Alzheimer's disease, these tend to occur at the depths of sulci in the early phases of the disorder, and then become more widespread, potentially becoming widespread by templating and spread. And there are few or no noridic (sp) plaques seen in this condition. There have been occasional instances of CTE being described with motor neuron disease as well.

Dr. Ann McKee at Boston University has the largest series of CTE autopsy examinations, and she's proposed a pathological criteria for this disorder including a perivascular foci of hyperphosphorylated tau in neurofibrillary tangles, so around the blood vessels, an irregular cortical distribution of the hyperphosphorylated tau with a predilection for the cerebral sulci, and the depths of the sulci. But within the cortical ribbon itself the accumulations tend to be in the superficial layers of the cortex. There are also accumulations of sub-pearl and periventricular astrocytic tau. And we're increasingly recognizing the roles of astrocytes in the protein disorders of the brain.

And this shows the proposed temporal progression of this disorder. Initially there may be focal isolated little accumulations of phospho tau, possibly completely asymptomatic or associated with early executive dysfunction or affective issues. Later on the tau spreads a bit more, again remaining more at the depths of sulci, but adjacent areas may show the hyperphosphorylated tau. And then in the very advanced stages, there's fairly widespread but non-stereotypic distribution of the phospho tau in astrocytes and neurons.

So the unique features we've described of CTE histopathology appear to be the distribution of the neurofibrillary tangles in the sulci, (inaudible) depths in the superficial cerebral cortex, and in a perivascular distribution.

Now there are other findings. There is diffuse axonal injury in all cases described thus far. Amyloid beta deposition does occur in a substantial fraction, however this is mostly in the form of diffuse plaques and perivascular distribution, which is different from the compact plaques or noridic plaques we see in Alzheimer's disease. We also see accumulation of a protein called TDP43 in over 80% of the cases. Now TDP43 is a common protein seen in neurodegenerative disorders. It binds both DNA and RNA and is responsible for transcriptional regulation. It is normally a nuclear protein, but in pathogenic forms it will migrate to the cytoplasm and is hyperphosphoralated, so very reminiscent of what is seen in TAL. And TDP43 is seen in front of temporal dementia, amytrophic lateral sclerosis, and in 80% of cases of CTE.

Also, CTE autopsy examinations, again mostly by Dr. McKee, show significant comorbidity. Up to almost 40% of the patients will have additional neurodegenerative disorders, including Alzheimer's disease in ten percent, motor neuron disease, frontal lobe degeneration and Parkinson's disease in a handful.

So there are some serious unknowns about CTE. What is the incidence? We simply don't know. The autopsy series I've described have severe case ascertainment bias, and there are only a handful of neuropathologists who have seen these cases, and many of the cases now are being referred to Boston University in particular, but that leads to case ascertainment bias.

It does appear CTE is rare, because if we informally polled brain bankers at the NIH meeting that Don mentioned earlier, most said they've either never seen it or very rarely seen neurofibrillary tangles not in the context of Alzheimer's disease.

Also, Dr. McKee's autopsy series uses extremely elaborate whole-brain slices with detailed immunohistochemical examinations, which we do not normally do in the course of examination of a brain.

Is repetitive TBI required to produce CTE? Probably so. And it looks like single hits are probably different from chronic hits, repetitive hits, with single hits being associated with beta amyloid and chronic neuro inflammation. We simply don't know the magnitude of forces, duration, frequency, or number of hits required. We're beginning to learn a little bit about the genetic background, and Dr. Zukowski will mention that briefly.

So what do we do? Well, tau imaging is on the horizon. Reliable (inaudible) methods for quantitating tau are in development and are beginning to be used. Some older methods are not reliable and should not be used, but these may complement the amyloid imaging. We need more autopsy series with less ascertainment bias. Epidemiological studies in sports and the military.

What do we do in the meantime? I would suggest that the concussion and blast guidelines that have been developed are a very good start. We have to stay objective and critical as the evidence emerges. And most importantly, as in all things, don't panic, and carry on.

Thank you very much.

Thank you, Clay. That was outstanding and gave us a really nice underpinning of pathobiology of tau proteinopathies and their association with TBIs.

I want to remind everyone who is on the webinar to please be typing in your questions for our speakers today, and as I said before, we'll try to get to as many of those as we can.

So the next speaker is a former colleague of mine at the University of Pittsburgh, who really taught me, I think, a lot about the similarities of Alzheimer's disease and some of the pathologic markings in TBI. Dr. Stephen Zukowski just finished his tenure as Dean of the School of Medicine at the University of Virginia. He is Professor of Neurology, Psychiatry and Neurobehavioral Sciences. He is co-founder of the Alzheimer's Disease Research Center at the University of Kentucky. Director of the Alzheimer's research program at the University of Pittsburgh, and Chair of Neurology before he was appointed Dean at the School of Medicine at UVA. He just finished that and is now a Visiting Professor at the University of Pennsylvania. And I think most important, or very importantly, Dr. Zukowski was instrumental in helping to, number one, understand and define some very early findings on CTE that Dr. Bennet Omalu at Pittsburgh had described in a paper in, I think, 2005. And also Dr. Zukowski was coauthor on a paper, the first paper I'm aware of, that described PET imaging for amyloid in Alzheimer's disease. And so as part of his talk I'm also hoping that he'll talk to us about creating morbid imaging for CTE. And so with that, Steve, I'll turn it over to you.

Thank you very much, Don. Also I'd like to thank the office for all of the aid in the organization that we had in putting these pieces – these three, we hope, complementary talks together. I'm going to try and draw on some of the information from both Dr. Hovda's and Dr. Goodman's excellent talks to give a slightly higher view but with a bit of integration that will tell you not only some things we think will be hopeful about the process, but also about where the direction of research and clinical application is going as we look at all of these data from molecular biology to clinical observations that so many of the audience is involved with every day.

I have no relevant financial disclosures. I will not be discussing any off-label use of commercial products or devices, but I will have a discussion about, as Dr. Marion indicated, the potential for subclinical or pre-clinical evaluation with imaging of pathological changes.

The major questions I think we'd like to try and integrate things and answer here is, what is the relationship of the blast and concussive injury to the longer term cognitive outcomes? CTE is the most dramatic of those and probably the most new one to be discovered, or we should say re-discovered since we believe it is significantly similar to dementia pugilistica or boxer's dementia. How do the clinical and the neuropathological changes relate to Alzheimer's disease or other neurodegenerative diseases? Dr.

Goodman has given an excellent summary of some of the pathology, but I think we'll compare and contrast a bit of the behavioral and the neuropathological changes in the course of trying to understand this. And finally, how can we treat it or how can we prevent it? And in these cases you'll see, I think, Alzheimer's research has emerged not just to look at the effects of CTE and longer-term disease, but also because of the focus on tau has entered the Alzheimer's researchers have really helped us in terms of traumatic brain injury understanding the path of biology, both shorter and long term.

One of the issues about getting your arms around traumatic brain injury is the fact that there are lots of things that happen in brain trauma. A number of those complexities from a biophysical standpoint, Dr. Hovda commented upon. But we can break them up grossly into two big categories. The first would be an acute single incident trauma, such as an automobile crash, or a single very severe blast injury with concussion with decompression, being blown and hitting some other object, which we know leads to the acute accumulation of amyloid deposits, what are called diffuse plaques, just a gathering, and I'll show some of these, of amyloid. And we know that these single acute severe injuries increase the long-term risk to develop Alzheimer's disease. Importantly they don't guarantee it, but they do appear to address the risk.

The second kind of injury is one if you take a history of not a severe auto crash, perhaps 15 or 20 years before, but the repetitive injuries which are less severe, such as those seen in boxing and football and certainly in combat. We don't know the acute pathology fully, in large part because these are less severe injuries, fortunately there is not a lot of autopsy material available. We do know, as Dr. Goodman pointed out, that the chronic pathology following repetitive injuries is tau or neurofibrillary tangle based. The neurofibrillary tangle data being known from the 1920s. And the clinical spectrum of long-term outcomes includes a variety of things. Some of the varying proteins Dr. Goodman discussed, but we see dementia, CTE most prominently, Parkinsonism, and ALS or other motor disorders, and of course the major issue now is what is chronic traumatic encephalopathy, and, indeed, as Clay started to discuss, what is the likelihood that someone would develop this given that they'd had trauma in the past.

So this is an image meant to discuss these issues a bit more, and you can take time to look at it or look in the reference below from *The New England Journal*. Mild traumatic brain injury is one in which with best outcome there is some difficulty over time. Dr. Hovda described that. Mild traumatic brain injury which is repetitive, perhaps within the vulnerable phase as described by Dr. Hovda, it will occur more severely and long term, but we do know that it leads to the long-term neuropathological changes that Dr. Goodman described that are talked about by Dr. McKee in her neuropathology descriptions of CTE as well as by Dr. Omalu and his colleagues.

And then the single severe TBI or course presents predominantly with severe injury, usually coma, complexed with whatever other trauma may have occurred, whatever the injury was it was severe, and then may lead, as discussed before, too, a chronic neurodegenerative disease, and this is one of the things we want to discuss.

The variability isn't just in terms of how you can have an injury, but the outcomes, which we are most interested in as clinicians, are variably affected by a number of other issues. The foremost of these, certainly in late life to mid-life, is age. The second is the temporal proximity of repeated TBIs as well as the number of TBIs. The illustration shows basically the effect that Dave Hovda showed in his earlier study that it takes longer to recover if you've had multiple injuries versus one. But this one goes on to show when you would have longer-term outcomes being affected and basically shows that single severe injuries, or even multiple small traumatic brain injuries, may lead to the emergence of clinical symptoms later in life. And why that occurs is one of the things that we want to discuss specifically.

The severity of the injury, how much trauma there is, Dr. Hovda made the correct point about ischemia not relating to the mechanism of TBI itself, but with a poly-trauma victim, blood loss, autonomic disregulation, there may well be associated ischemia with an injury that involves a car wreck or an injury in wartime. So the breadth and the extent and the nature of the lesions, are they ischemic, are they directly related to trauma, is there a hemorrhage which has produced ischemia by compression or other damage, all of these things yield a high variability of the disorder that is something we want to make sure we understand.

Now we also know that the genetic – and we're just getting to the start of this – genetic outcomes can affect what happens to people who have trauma, and one of these turns out to be a lipoprotein gene, apolipoprotein e genotype, one particular type which is also a risk factor for Alzheimer's disease, appears to worsen outcome. And I'll talk more about that in a moment.

There are also other genetic factors which relate to the injury's response to the inflammation which Dr. Goldman indicated was becoming more of a significant factor in understanding trauma as well as chronic neurodegenerative disorders and one's ability to regenerate or repair in the face of injury.

Study designs have to consider all of these possible variabilities, which increases the number of people needed for a study and also the duration of time that they need to be followed, and this is one of the reasons why it has been such an issue for us to mount up quickly studies that give us accurate answers about outcomes and prevention.

Repetitive TBI and risk of long-term disease in football, soccer, hockey, boxing, rugby, have all been fosci of short and long-term risks. Dr. Goodman commented that we know that there is not a lot of experience with CTE on the basis of neuropathologists. One reason for that may be, of course, that it is very rare. Another, although I do believe it is relatively uncommon, is that in routine pathological examinations of brain, although most neuropathologists do more, we don't stain for neurofibrillary tangles or for other kinds of fibrilar abnormalities and you need to use special stains, as he hinted before. Looking for some evidence or global estimate of what the risk would be of an outcome of repetitive TBI, the best we can do so far is the fact that in these early studies in the 20s, 30s, 40s, it looked as if about 20% of the boxers who were evaluated developed dementia pugilistica after boxing careers. And because of the ascertainment bias that Clay mentioned, it's quite likely that we are seeing much more CTE than actually occurs. It isn't true, certainly, that everyone who has repetitive injuries gets the disorder, but we need to know what are the risk factors and what are the prevention or protective factors.

We know that long-term neuropsychological impairment correlates with the number of rounds boxed by boxers, not necessarily with their won-loss record, which means that multiple TBI clearly increases your risk. And we also know that the severity of the impairment in boxes relates to the apo e genotype. There are three aleals of apo e, perversely named epsilon 2, epsilon 3, and epsilon 4. Epsilon 3is the most common form. But E four, which turns out to be a risk factor for the development of Alzheimer's disease, is also the one that appears to worsen outcome of multiple injuries in boxers.

We also know that in the CSF, as Dr. Goodman mentioned, there are markers of brain damage, including neurofilament protein N tau, which are increased in boxing, again, independent of whether there was a knockout or not. Just boxing three rounds will increase these, as it will increase a beta, which is the issue for Alzheimer's.

How does it work in Alzheimer's disease? We know more about apo E in AD since it was discovered as a risk factor in the early 1990s. Apolipoprotein e carries cholesterol, that's its job, in the periphery which is necessary, cholesterol, for normal metabolism and brain repair. Chromosome 19 is where apo e is. It has the three aleals I mentioned. And it also serves, although it carries cholesterol, it also serves to remove beta amyloid, the fragment peptide which is abnormally elevated in Alzheimer's disease, from the central nervous system. It links to a protein called LRP 1, and that's how it gets out of the brain and into the blood to be removed via the kidney. Apo e is not as effective in this mechanism of removing beta amyloid from the CNS as is the apolipoprotein made if you are carrying the apo three aleal or the apo two aleal.

A single aleal of e 4, remember you get one from your mother, one from your father, a single aleal of e 4 triples the risk of someone to develop Alzheimer's disease in late life. And if you are a homozygote, which is only about two percent of the population, homozygotes have an eight to 12 time risk of developing the disease.

And in Alzheimer's disease, we believe that the buildup of A beta, the beta amyloid, which is what the plaques are made of, is facilitated by slow removal of A beta from the brain, and apo e 4 four developed apolipoprotein e is not as good at removing it. This is one of the reasons we think it may be risky.

Well how does that relate to brain trauma? Well, there was a discussion at meetings in Keystone about a year-and-a-half – no, two years ago, where a gathering of people doing research on apo e and brain trauma were surveyed to ask whether they thought there was enough information from the boxing data and from the Alzheimer data to do apo e testing on people who might be at risk of traumatic brain injury. The short answer was no, there was not enough data to extrapolate this for decisions regarding sports or armed forces, but interestingly, these 50 or so researchers said that if they happened to come by the information in some other way, that they would use that information to make guidance for their own families. So we truly are at a point where we are trying to decide what to do while trying as quickly as we can to get data. And as many of you know, there are ways you can have this done commercially. There are risks, of course, associated with having genotype information available in your medical record, and so we have not quite decided where this will go.

That brings us, though, to what's the relationship of amyloid to neurofibrillary tangles and TBI? We know that after brain trauma there is an upsurge of APP and A beta after severe injury, one of the several proteins that goes flying up. Amyloid plaques form acutely in 40% of people with the severe TBI, such as an auto accident. Pathology studies, as well as some biopsy studies taken to remove tissue, or hemorrhage, or to decompress the brain if it's swelling, confirm the presence of plaque. You don't see neurofibrillar pathology at this time. But there is a question of whether the neurofibrillar pathology that occurs in Alzheimer's is led from the development of amyloid in the brains of subjects, or do the neurofibrillary tangles in chronic traumatic encephalopathy form by a different mechanism, as has been proposed secondary to axonal disruption and the subsequent spread from neuron to neuron templating, or do both of them account for the pathology of TBI.

This is a slide from a biopsy of a patient within two hours of brain trauma, a 33-year-old person, which shows that both APP and amyloid, that is amyloid precursor protein and beta amyloid, are both increased acutely in trauma. And amyloid plaques can be seen within hours of injury, even in young people for whom incidental development of Alzheimer's disease wouldn't be a complicating factor. So we know that there is amyloid there. In boxers it's elevated, probably not to the level of plaques, but both the plaques and the soluble beta amyloid are present in the brain.

So how does acute trauma lead to neurofibrillary tangles such as Clay discussed? Well, we know that the distribution of neurofibrillary tangles is different than the laminar pattern which is predominantly in the lamina three and five of the cortex. And it's largely in a number of layers, although you can see in this picture on the right from Ann McKee that it does predominate in those layers, but that's also because the big paramable (sp) cells are there. But this distribution at the bottom of the creases in the brain, the bottom of the wrinkles or the sulci, is different than Alzheimer's disease. You do not see that sort of isolation within the lower areas of the brain.

The mechanisms of the longer-term cognitive and neuropsychiatric symptoms is unknown. We do know there is more early neuropsychiatric symptoms that show in brain trauma than there is in CTE than there is in Alzheimer's disease. But we also know that disrupted tau metabolism is accompanied by axonal loss due to torsion and axonal sheer. There are genetic as well as epigenetic vulnerabilities. There's regional cell and neurotransmitter system loss and disruption. These will be both variable and, obviously something happens that leads to ongoing pathology that eventually emerges as a clinical symptom.

Two global hypothesis, that the first is we lose our reserve, that is our ability to withstand any kind of tissue damage with the ability to maintain normal cognition, because of all the injury-induced structural losses. Both the acute losses that Dr. Hovda spoke about, we lose neurons, we lose axons, we have neurofibrillar disruption and disconnection of different areas of brain one from another. There may be ischemia as a secondary or associated problem, not from the primary TBI mechanism itself. But the loss of cognitive means that as one gets older and things change, and there are all sorts of normal aging changes, that what happens is because you have less reserve, the disease emerges sooner than it might otherwise, or might emerge in someone who was never destined to have a cognitive impairment if they'd had their full cognitive flexibility that they were born with.

The other option, however, which has important implications for treatment, is the cortical beta amyloid up regulated with multiple injuries drives the pathology in AD, in CTI – sorry, with CTE, but then because the injuries may have occurred, let's say, in a boxer at age 30, the person has 20 years during which the amyloid would certainly be removed from the brain, even if they were an apo e 4, but the visible end stage pathology would involve tangles. And maybe one of the reasons this emerges is because the tangles are facilitated not only by the axonal and structural damage at the injury itself, but also with the evolution of neurofibrillar pathology produced by amyloid. Because mutations in beta amyloid or in its enzymes that leads to Alzheimer's disease all produces neurofibrillary tangles as part of the pathological cascade. And so there isn't a particular reason to think that multiple increases in beta amyloid in people at a younger age could not go on to develop neurofibrillary tangles. And we will find out about this.

Now we have the high variability of TBI and related injuries, the various ways it occurs. We know that there is regional neuronal death, axonal loss to neuropath classifications as pointed out by Clay, and we also know that there are comorbid neurodegenerative disorders and protein deposits, Parkinsonism and ALS and so forth. Cross-sectional studies don't equal longitudinal studies. And one of the reasons we need to follow people in research studies is to determine whether we can see things that we could not see when we just stacked the variable cases of severe injury or mild injury together with respect to findings. This is a place where biomarkers, especially blood and CSF and many new kinds of neuro imaging can both be, we hope, predictive in the short term of what we should do and how severe the injury is, but also with serial imaging, be able to determine whether certain kinds of therapy will be helpful. Because not only treatment but now also prevention of long-term adverse outcomes are a focus, and we're hoping that we would be able to learn enough to be able to look at people at risk for the development of the later neurodegenerative changes and utilize medications, some of which are surely going to come from TBI research and, ironically, some of which even in younger people, may well come from Alzheimer's disease research.

It used to be, and some of you are old enough to remember, that neuropathology and a clinical pathological correlation after death was the standard way that we got a pathological understanding of clinical findings. The autopsy was king. If you had a patient with a disorder, you had to wait until they had passed away to get the pathology. There were no prospective studies done, obviously, and the longitudinal and serial protein images of PET and MR have now changed the paradigm whereby we no longer have to worry about the issue of waiting until someone dies, perhaps decades later, to know.

This is a study that shows you some of the benefits, at least, of a serial studies of single points. This is the evolution of neuropathology of tangles in Alzheimer's disease. And as Dr. Goodman pointed out, this is not the same as it is in Alzheimer's. But this is now one of the new tau markers, T8 07, which shows you the development and the visualization in a living patient of neurofibrillary tangles in the brain of patients who are normal and in people developing Alzheimer's disease. This has not yet been extensively utilized in chronic traumatic encephalopathy, or indeed even in people at various times after chronic traumatic brain injury, after brain injury, but this will be and these studies are now all under way. This gives us the opportunity not just to wait until someone has passed away to learn, but be able to not only make predictions but follow people and intervene.

So we know that the main genetic risk factor for Alzheimer's, which increases brain accumulation of beta, also increases the risk of chronic traumatic encephalopathy and the severity of outcome. We also know that a number of A beta lowering agents, statins or gamma secretase inhibitors, one of the early kinds of interventions trying to slow amyloid, is an outcome that we would like to see applied in humans. Many of these drugs, both anti tau and anti amyloid drugs, being developed for AD we hope to apply in TBI. And longitudinal assessment for both of these will provide directions for improved interventions.

So understanding the time course, getting the biomarkers available promotes single short-term and longer-term outcomes as well as determining what gives one person this kind of pattern and the other are all issues of study for which we now believe we have both biochemical and imaging tools that will let us answer questions which we never could answer before.

Thanks very much.

All right. Thank you very much, Dave, for an excellent overview and sort of tying things together, and especially those comments about imaging.

So we've come to the point in this webinar for the questions, but before we begin, I would like to provide a brief introduction to the progressive return to activity clinical recommendations. It's a product that the Defense and Veterans Brain Injury Centers produced, particularly Dr. Terese West (sp). I am pleased to announce this new clinical recommendation is being released next Wednesday, January 22nd. It is designed to help patients who have sustained an acute concussion or mild traumatic brain injury to progressively return to their normal activities following injury. The progressive return to activity following acute concussion/mild traumatic brain injury guidance for the primary care manager and the rehabilitation provider in deployed and non-deployed settings clinical recommendations will be available at our website at dvbic.dcoe.mil.

So what these are are two separate clinical recommendation packages. And they're tailored for either primary care managers, or the second one for rehabilitation providers. And they consist of four products each. A clinical recommendation, a clinical support tool, a provider education and slide deck, and a patient education product.

These guidelines were developed with input from academic experts, (inaudible) concussion clinicians, and military TBI experts. And they will assist healthcare providers as they monitor patients recovering from concussion.

The Progressive Return to Activity Clinical Recommendations are the first of their kind. They are tailored for primary care managers and rehabilitation providers, and offer a standardized clinical approach for service members who have sustained an MTBI to allow them to return to activity in a monitored way and to optimize recovery. And incidentally I think they fit very nicely into this information we've learned today, especially from Dr. Hovda. The recommendations give providers and patients a practical how-to manual for concussion recovery by clearly describing a gradual (inaudible) return to activity after a period of rest.

So, again, these products are downloadable, and I'll repeat that. It's dvbic.dcoe.mil.

All right. So it's now time for questions from the audience. We are monitoring the Question box and will forward questions to our presenters for a response. If you've not already done so, you may submit your questions via the Question box, and we'll respond to as many as we can.

So the first question is for Dr. Hovda, and I actually is interested in the answer to this, too, Dave. One of our webinar participants asks given what you've shown, should we be providing a high sugar diet, such as grape juice, to service members immediately after their concussion, or conversely, do you have a problem with giving them a Red Bull immediately after their concussion? So Dr. Hovda.

Well, can you hear me?

Yes.

Okay. The answer to both those questions is probably not. The problem with the sugar is that when you label sugar, and you give it to a brain after it's been injured, the sugar and glucose is actually being used for something other – part of it is being used to turn on genes and proteins and not necessarily to increase the energy supply to the brain. Other fuels are being explored like lactate, or pyruvate, or ketone bodies that may be able to provide some effect for these individuals.

Red Bull or stimulants after traumatic brain injury can be contraindicated. When you think about the amount of activity that an individual would endure after they've had a concussion. At this particular point in time, we have a little bit of basic science evidence – I have no clinical evidence that I can cite – that just says an increase in activity by itself would increase cell death within the brain. The basic science studies would suggest that it makes the brain worse, and it actually creates a loss of plasticity and a more compromised central nervous system.

There are some clinical studies that have looked at things that have to do with memory and learning and neuropsychological studies after traumatic brain injury when individuals are exposed to higher levels of cognitive or physiological functioning too soon after their concussion, and they do deteriorate. But I don't believe that there's been any studies looking specifically at cell death.

Thank you, Dave.

The next question is for Dr. Goodman, and the question is, the tau changes you described , Dr. Goodman, and the degeneration, is that permanent or is there a possibility of reversal of the protein deposition?

Oh, thank you. That's a wonderful question. For many years we thought that the inclusions were basically a dead end and they could not be mobilized, but it does appear that some of the tau may be mobilizable from the inclusions. Now that's a double-edged sword because if it is mobilized and goes back to the fibrillary form, the ultra structurally visible forms, those are probably the most toxic forms. So the inclusions may serve as a depot for these toxic forms of tau.

On the other hand, there has been quite a bit of work in Alzheimer's disease attempting to facilitate the mobilization of beta amyloid. So the therapeutic strategy is likely sound and may be applicable to tau.

And what would that therapeutic strategy be again?

Well, for tau, unknown at this point. There have been in some other proteinopathies attempts to prevent the fibrilization by putting little molecules that prevent intercolation between the fibrils, those had fairly poor results. But to mobilize tau, I'm not aware of any drugs that are immediately on the horizon to do that.

For the beta amyloid, it's been an antibody strategy, largely, to try to mobile the beta amyloid.

Great. All right. The next question is for Dr. Zukowski. Is there a connection between migraines and multiple concussions, and as a corollary to that, does tau have any effect on the severity of the migraines?

Tau, itself, isn't known to have any effect on migraines, the migraine abnormalities. Maybe since many people report worsened migraines after trauma may relate to disordered vascular reactivity and disordered neurotransmitter function in brain. But certainly chronic headaches and sensitivity occur after brain injury.

I would like to just make a quick follow up to Dr. Goodman's comments about the therapies, the Alzheimer therapies for tau, as he said, are largely going to be directed toward prevention. But just because they become hyperphosphorylated in the course of becoming abnormal, a number of medications that would block the hyperphosphorylation, we know what the enzymes are that do that, they are in clinical trials. And there are some clinical trials of anti tau drugs being used in Alzheimer's and the TBI field is looking at these very carefully to see what, from a toxicity or from a potential applicability standpoint, they could be used in TBI.

All right. And so as long as we've gotten into therapy a little bit, there are a number of questions about hyperbaric oxygen and oxygen free radicals, and so maybe Dr. Hovda, you could comment on the role of free radicals and acute pathophysiology after mild TBI and the advisability of treatment with HBO.

Sure. I get that question a lot. There is hyperbaric oxygen was, you know, is very effective for many different types of injuries to the body, burns and skin lacerations, and what not. I think the literature there is very solid.

When it was originally designed for head injury, which was by Dr. Roxwell (sp) many, many years ago up at the University of Minnesota, it was primarily used for acute traumatic brain injury, and it was only used in severe traumatic brain injury. And in those particular studies, there was some evidence to suggest that hyperbaric oxygen did improve. Remember that the concept of hyperbaric oxygen is just to try to bring the oxygen tension of the blood up to increase the delivery of the oxygen to the central nervous system. The concept of whether oxygen gets to the central nervous system is one thing. Whether it can be utilized, whether oxygenated metabolism goes up, is a completely different story.

There have been studies in literature where people have reported a few case reports, and I've seen a couple of prospective studies where they've put people in a hyperbaric oxygen chamber that have long-term post-concussive symptoms, and the patient's self-report is that they feel better. In terms of the physiology, if the mitochondria are dysfunctional and the mitochondria are having a difficult time respirating, whether the oxygen is there or not, it won't be oxidized appropriately.

The comments about free oxygen radicals are very important. Oxygen free radicals are something that actually occurs quite normally in normal physiology in the brain. You can think of it in the layman's way of thinking of a very toxic like hot (inaudible) that you would put into the tissue that would actually eat the tissue or damage the membranes. And there are ways of buffering these free oxygen radicals which we normally have. And the question of all trauma to the central nervous system, whether it be biochemical trauma, or ischemia, or other types of stress, is the fact that these capabilities of the central nervous system to protect itself from free oxygen radicals is overwhelmed. And then they actually begin to degrade the tissue and kill the cells from the inside out.

So the utilization of hyperbaric oxygen at very low dives of 1.5, that I've seen. I've seen as high as two. We haven't seen anything that would suggest that it would be harmful for individuals. But we haven't been able to put our fingers on whether it actually is beneficial because if it, in fact, produces an increase in oxygen metabolism.

There are a couple of really beautiful studies that have been done that have controlled for this. And it doesn't appear that the oxygen saturation in the blood is critical to the effects patients are reporting with hyperbaric oxygen therapy.

All right, so, Dave, if I can just paraphrase a little bit. So you're telling us that even though you have these – this metabolic mismatch in concussions similar to what you see in severe TBI, that it's a problem with the mitochondria being clogged up with calcium so that they're incapable of using the potential increase in ambient oxygen you might get with HBO. Is that fair?

That's fair. The mitochondrial – it's called mitochondrial dysfunction. And this doesn't occur all at one time. And calcium accumulates in the cells over the course of hours to days after a mild traumatic brain injury. So one could think – although I haven't seen this study done – that if hyperbaric oxygen was provided very soon, whether in fact there would be enough mitochondrial support to utilize it, and whether that would tip the balance to producing more ATP in order to help the mitochondria survive, whether, in fact, that would be the case. I just haven't seen it. And I've seen that the, in at least experimental studies that people have looked at, as well as in the human studies when we looked at oxygen metabolism, it just seems to be depressed after even mild traumatic brain injury and stays depressed until the mitochondria are ready to recover.

All right. So I'm being told by my handlers here that we have to wrap it up, so I want to thank all of the presenters again, Dave, Clay, and Steve. You guys were great, and it was so good to work with you.

To help us improve future webinars, we encourage you to complete the feedback survey that has been opened in a separate browser on your computer.

To access the presentation and reference list for this webinar, you may download them from the files below or at dvbic.dcoe.mil/online-education.

An audio recording and edited transcript of the closed captioning will be posted to that link in approximately one week.

The next DCOE psychological health webinar topic is Sleep Disturbance Assessment and Evidence-Based Clinical Interventions in the Active Duty and Veteran Populations, and it is scheduled for January 23rd from 1:00 to 2:30 p.m. Eastern Standard Time.

The next DCOE traumatic brain injury webinar topic is Joint Theater Systems Practice Guidelines and Recommendations and is scheduled for February 13th from 1:00 to 2:30 p.m. Eastern Standard Time.

So we've run out of time. I want to thank you again for attending and have a great day everyone.

Thank you for your participation. That does conclude today's conference. You may disconnect at this time.